REMARKS

A check for $1720 for the fees for filing of an RCE ($770) and for the fee for a three-month extension of time ($950) accompanies this response. Additional fees were previously paid in this application for two (2) additional independent claims (a total of five) and an additional sixty-seven (67) claims (a total of eighty-seven). Therefore, no fee should be due for the two (2) independent claims and thirty (30) dependent claims added herein. Any fee that may be due in connection with this application may be charged to Deposit Account No. Deposit Account No. 06-1050. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Claims 1-53 are presently pending in this application. Claims 1 and 5-8 are amended and claims 22-53 are added herein. Claims 1 and 5 are amended to more distinctly claim the subject matter. Basis for the amendment can be found throughout the specification (for example, see page 7, lines 1-3). Claim 6 is amended to correct dependency necessitated by the amendment of claim 5 herein. Claims 7 and 8 are amended to replace the word "site" with the word –group– in order to more distinctly claim the subject matter and to avoid any ambiguity. No new matter is added.

Basis for added claim 22 can be found throughout the application (for example, see page 38, lines 18-26). Basis for added claim 23 can be found throughout the specification (for example, see page 8, lines 19-27; page 33, lines 25-26; and FIG. 5E). Basis for added claims 24 and 45 can be found throughout the specification (for example, see page 16, lines 5-7 and claim 18 as originally filed). Basis for added claims 25 and 47 can be found throughout the specification (for example, see page 16, line 7 and claim 19 as originally filed). Basis for added claims 26 and 46 can be found throughout the specification (for example, see page 16, lines 19-21 and claim 20 as originally filed). Basis for added claims 27 and 49 can be found throughout the specification (for example, see page 9, lines 7-8 and claim 12 as originally filed). Basis for added claim 28 can be found throughout the specification (for example, see page 9, lines 7-8 and claim 13 as originally filed). Basis for added claims 29 and 50 can be found throughout the specification (for example, see page 9, lines 4-6 and claim 14 as originally filed). Basis for added claims 30 and 51 can be found throughout the specification (for example, see page 9, lines 4-6 and claim 14 as originally filed). Basis for added claims 31 and 52 can be found throughout the specification (for example, see page 16, lines 14-15 and claim 16 as originally filed). Basis for added claims

32 and 53 can be found throughout the specification (for example, see page 16, lines 15-16 and claim 17 as originally filed).

Basis for added claim 33 can be found throughout the specification (for example, see page 6, lines 12-22). Basis for added claim 34 can be found throughout the specification (for example, see page 6, lines 23-24 and claim 2 as originally filed). Basis for added claim 35 can be found throughout the specification (for example, see page 6, lines 24-25 and claim 3 as originally filed). Basis for added claim 36 can be found throughout the specification (for example, see page 6, lines 24-25 and claim 4 as originally filed). Basis for added claims 37-40 can be found throughout the specification (for example, see page 7, lines 1-6, and claims 5-8, respectively, as originally filed). Basis for added claims 41-44 can be found throughout the specification (for example, see page 7, lines 1-6, and claims 5-8, respectively, as originally filed). No new matter is added.

THE REJECTION OF CLAIMS 1-15 AND 18-20 UNDER 35 U.S.C. §102(e)

Claims 1-15 and 18-20 are rejected under 35 U.S.C. § 102(e) as anticipated by Hiatt *et al.* (U.S. Patent 5,763,594) because Hiatt *et al.* allegedly discloses a nucleic acid primer having a first region containing the 5' end of the primer and an immobilization attachment site, and a second region containing the 3' end of the primer and a chemically cleavable site, where the 3' end is capable of being extended by an enzyme. It is further alleged that although Hiatt *et al.* does not disclose that a second region of the primer contains a selectively chemical cleavage site, the 3' end of the nucleic acid of Hiatt *et al.* allegedly is selectively cleaved with 1M piperidine and therefore the Examiner urges that Hiatt *et al.* anticipates the limitations of the claims.

This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir. 1990); *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990); Soundscriber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl. 1966). *See, also, Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover, it is incumbent on the Examiner to identify where each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and*

Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

THE CLAIMS

Independent claim 1 is directed to a nucleic acid primer that includes a first region containing the 5' end of the primer and an immobilization attachment site; and a second region containing the 3' end of the primer having a free 3' hydroxyl and a selectively chemically cleavable site, where the 3' end is capable of being extended by an enzyme to generate an extension segment and the selectively chemically cleavable site includes a modified sugar or a chemically cleavable group incorporated into the phosphate backbone. When the primer is immobilized via the immobilization attachment site, and the selectively chemically cleavable site is cleaved, the remainder of the primer remains immobilized. Claims 2-15 and 18-20 depend from claim 1 and are directed to various embodiments thereof.

Disclosure of Hiatt *et al.*

Hiatt *et al.* discloses a method for the synthesis of a polynucleotide of a predetermined sequence where the 3'-hydroxyl group of a deoxynucleotide triphosphate can be protected and deprotected for use by a template- independent polymerase to extend the initiating substrate a predetermined sequence (col. 4, lines 5-15). Hiatt *et al.* discloses removable blocking groups, including carbonitriles, phosphates, carbonates, carbamates, esters, ethers, borates, sugars, phosphoramidates and others that block the 3' position and when removed produce a hydroxyl group at the 3' position (col. 4, lines 59-67 and col. 10, lines 21-62). Hiatt *et al.* discloses an initiating substrate terminated by a deoxyguanosine methylated at the 7 position of the base and directly attached to a solid support (col. 17, lines 51-63).

ANALYSIS

The Examiner alleges that Hiatt *et al.* discloses the claimed primers, and cites col. 17, lines 51-67; col. 18, lines 1-20 and col. 4, lines 61-67 as basis. Applicant respectfully disagrees. Column 17, lines 51-67 and col. 18, lines 1-20 of Hiatt *et al.* discloses:

> Cleavage of a newly synthesized polynucleotide strand from the solid support and/or from the initiating substrate can be accomplished by either chemical or enzymatic reactions. In the case of a chemical reaction, if the initiating substrate terminal nucleoside (containing the free and unmodified 3'-hydroxyl group) is a deoxy-guanosine methylated at the 7 position of the base:
>
> Support-dCCCCCCCCCCC-Me^7-G-object polynucleotide (SEQ. ID No. 1)

> reaction with 1M piperidine in water at 90°C will cleave the chain at this position yielding only the desired polynucleotide in solution. This method can yield a polynucleotide chain containing only the predetermined sequence and can be performed either on immobilized chains (to effect cleavage) or on solution synthesized chains to remove the initiating substrate. Alternatively, the dG^{7me} can be positioned at any location within the initiating substrate or the object polynucleotide where cleavage is desired. Other examples of modified base-specific cleavage of polynucleotide chains have been extensively described in the literature (See, Ambrose and Pless, *Meth. Enzymol., I* Vol 152: 522-538.)
>
> Enzymatic removal of the polynucleotide chain may be accomplished by reaction with a specific restriction endonuclease. For example, if the initiating substrate oligonucleotide has the following structure:
>
> Support-dCCCCCCCCCCCCCCCCTGCA-3'-OH (SEQ ID No. 2)
>
> and the object polynucleotide begins with a G, the resulting newly synthesized chain can be cleaved from the support by reaction with Pst 1 restriction enzyme. This method assumes there are no additional Pst 1 restriction sites in the newly synthesized chain and that one has annealed an appropriate oligonucleotide to the Pst 1 site to render it in a double stranded form for recognition by the enzyme (e.g. an annealing oligonucleotide with the following structure:
>
> 3'-dGGGGGGGGGGGGGGGACGTC-5' (SEQ ID No. 3) for the example above).

Thus, Hiatt *et al.* discloses that an oligonucleotide containing a deoxyguanosine methylated at the 7 position of the base can be cleaved with 1M piperidine in water at 90°C at the dG^{7me} position of the oligonucleotide (col. 17, lines 54-61). Hiatt *et al.* also discloses that other examples of modified base-specific cleavage of polynucleotide chains are described in the literature (col. 18, lines 2-6). Hiatt *et al.* does not disclose primers that include as a selectively chemically cleavable site a modified sugar or a chemically cleavable group incorporated into the phosphate backbone.

The Examiner alleges that col. 4, lines 61-67 of Hiatt *et al.* discloses a modified sugar or a chemically cleavable group incorporated into the phosphate backbone as a selectively chemically cleavable site. Applicant respectfully disagrees. Hiatt *et al.* discloses at col. 4, lines 61-67 that:

> The methods of the present invention utilize removable blocking moieties that block the 3' position of nucleoside 5'-triphosphates used in the methods. Preferred removable blocking moieties can be removed in under 10 minutes to produce a hydroxyl group at the 3' position of the 3' nucleoside. Removable blocking groups contemplated include carbonitriles, phosphates, carbonates, carbamates, esters, ethers, borates, nitrates, sugars, phosphoramidates, phenylsulfenates, sulfates and sulfones.

Hiatt *et al.* does not disclose a modified sugar as a selectively chemically cleavable site in an oligonucleotide or primer. The Examiner appears to allege that the removable blocking group at the 3' end of the initiating substrate of Hiatt *et al.* is equivalent to the element "selectively chemically cleavable group" as instantly claimed. Applicant urges that this characterization is incorrect. Hiatt *et al.* defines its removable blocking group as a moiety that is attached to the oxygen at the 3' position of a nucleoside that prevents reaction of the 3' oxygen when present and is removable under deblocking conditions so that the 3' oxygen can then participate in a chemical reaction (col. 7, lines 12-18). Hiatt *et al.* discloses that its blocking group eliminates the free 3' hydroxyl group of the oligonucleotide, and it is only by removing the blocking group that a free 3' hydroxyl group is produced (see col. 4, lines 59-64). Applicant respectfully submits that if the "primer" of Hiatt *et al.* contains a 3' blocking group, then the oligonucleotide does not have a free 3' hydroxyl group as required in the instant claims. If the blocking group is removed, then the oligonucleotide disclosed by Hiatt *et al.* would have a free 3' hydroxyl available for use as a primer, but then the alleged "selectively chemically cleavable site" is not present.

The instant claims require both limitations – that the oligonucleotides be primers with a free 3' hydroxyl AND that the primers include a selectively chemically cleavable site. The oligonucleotides of Hiatt *et al.* have EITHER protecting groups (which the Examiner alleges is equivalent to the claim element "selectively chemically cleavable site") and no free 3' hydroxyl group OR they are deprotected and have a free 3' hydroxyl group but then do not have the alleged "selectively chemically cleavable site." They do NOT have both.

Thus, Hiatt *et al.* does not disclose a nucleic acid primer that includes a free 3' hydroxyl and a modified sugar or a chemically cleavable group incorporated into the phosphate backbone as a selectively chemically cleavable site. Therefore, the cited reference fails to disclose every element of the claimed subject matter. Accordingly, Hiatt *et al.* does not anticipate any of claims 1-15 or 18-20.

REJECTION OF CLAIM 21 UNDER 35 U.S.C. §103(a)

Claim 21 is rejected under 35 U.S.C. §103(a) as being unpatentable over Hiatt *et al.* in view of Köster (US 5,547,835) because Hiatt *et al.* allegedly teaches all elements of the claims except for a primer that is attached to the solid support by hybridization of the immobilization attachment site to the intermediary oligonucleotide single-stranded nucleic acid complementary to an intermediary oligonucleotide bound to the solid support, where the

primer is attached to the solid support, and Köster allegedly cures this defect. This rejection is respectfully traversed.

RELEVANT LAW

In order to set forth a prima facie case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would suggest to those of ordinary skill in the art" *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.* 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)).

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

CLAIM 21

Claim 21 ultimately depends from claim 1 and is directed to an embodiment thereof that includes a solid support, where the single stranded nucleic acid is complementary to an intermediary oligonucleotide bound to the solid support and where the primer is attached to the solid support by hybridization of the immobilization attachment site to the intermediary oligonucleotide.

Teachings of the Cited References

Hiatt *et al.*

See related section above.

Köster

Köster teaches a mass spectrometric method for sequencing using a Sanger sequencing strategy, in which one embodiment includes immobilizing the sequencing primers to a support using various linkers. Köster teaches that the primer has a linking functionality

L at the 5'-end that interacts with a suitable functionality L' on the solid support to form a reversible linkage L–L', cleavage of which removes the entire primer from the solid support (column 11, line 52 – column 13, line 2).

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of prima facie obviousness for the following reasons.

The combination of teachings of Hiatt *et al.* with the teachings of Köster does not result in the instantly claimed primers.

As discussed above, Hiatt *et al.* does not teach or suggest a nucleic acid primer that includes a second region containing the 3' end of the primer that includes a free 3' hydroxyl and a modified sugar or a chemically cleavable group incorporated into the phosphate backbone as a selectively chemically cleavable site, and Köster does not cure this defect.

Köster does not teach or suggest an oligonucleotide or primer having a modified sugar or a chemically cleavable group incorporated into the phosphate backbone as a selectively chemically cleavable site. Thus, Köster fails to cure the deficiencies in the teachings of Hiatt *et al.* The combination of teachings of Hiatt *et al.* and Köster does not teach or suggest a nucleic acid primer that has first region including the 5' end and a second region including the 3' end, where the second region has a free 3' hydroxyl and a modified sugar or a chemically cleavable group incorporated into the phosphate backbone as a selectively chemically cleavable site, such that when the primer is immobilized, and the selectively chemically cleavable site is cleaved, the remainder of the primer remains immobilized. Thus, even if Köster teaches capturing oligo-nucleotides to a solid support
via a complementary single-stranded nucleic acid, combining the teachings of Hiatt *et al.* and Köster does not result in the subject matter claimed in claim 21. Therefore, the Office Action does not set forth a *prima facie* case of obviousness, and the rejection should be withdrawn.

REJECTION OF CLAIMS 16 AND 17 UNDER 35 U.S.C. §103(a)

Claims 16 and 17 are rejected under 35 U.S.C. §103(a) as being unpatentable over Hiatt *et al.* in view of Edwards *et al.* (US 5,306,619) because Hiatt *et al.* allegedly teaches all elements of the claims except for a solid support that includes an anti-digoxigenin antibody, and Edwards *et al.* allegedly cures this defect. This rejection is respectfully traversed.

RELEVANT LAW

See related section above.

THE CLAIMS

Claim 16 depends from claim 11 and is directed to an embodiment where the solid support includes an antibody. Claim 17 depends from claim 16 and is directed to an embodiment where the antibody includes anti-digoxigenin.

Teachings of the Cited References

Hiatt *et al.*

See related section above.

Edwards *et al.*

Edwards *et al.* teaches a DNA:protein binding assay for screening libraries of synthetic or biological compounds for their ability to bind to a selected test sequence in a duplex DNA (col. 2, lines 58-62). The target oligonucleotide is labeled to allow detection (col. 4, lines 35-36). The label can be radiolabels or digoxigenin (col. 4, lines 36-41). In one embodiment, the target site includes digoxigenin as a label and a biotin moiety to interact with streptavidin attached to a solid support, and the target is detected using a tagged anti-digoxigenin antibody (col. 4, lines 44-50). In another embodiment, the target site includes biotin as a label and digoxigenin to interact with anti-digoxigenin antibody attached to a solid support, and the target is detected using tagged streptavidin (col. 4, lines 51-56).

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of prima facie obviousness for the following reasons.

The combination of teachings of Hiatt *et al.* with the teachings of Edwards *et al.* does not result in the instantly claimed primers.

As discussed above, Hiatt *et al.* does not teach or suggest a nucleic acid primer that includes a second region containing the 3' end of the primer that includes a free 3' hydroxyl and a modified sugar or a chemically cleavable group incorporated into the phosphate backbone as a selectively chemically cleavable site, and Edwards *et al.* does not cure this defect. Edwards *et al.* does not teach or suggest a modified sugar or a chemically cleavable group incorporated into the phosphate backbone of an oligonucleotide as a selectively chemically cleavable site. Edwards *et al.* does not teach or suggest an oligonucleotide or a primer that includes a modified sugar or a chemically cleavable group incorporated into the phosphate backbone as a selectively chemically cleavable site.

Thus, even if, arguendo, Edwards *et al.* teaches a DNA:protein binding assay where the target oligonucleotide is attached to the solid support using an anti-digoxigenin antibody that is attached to the solid support, combining the teachings of Hiatt *et al.* and Edwards *et al.* does not result in the subject matter of claims 16 and 17. Therefore, because the combination of teachings of Hiatt *et al.* and Edwards *et al.* does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

* * *

Entry of this amendment and examination of the application are respectfully requested.

Respectfully submitted,

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